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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/328,296	06/08/1999	CLAY B. SIEGALL	9632-005	6564

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EXAMINER
CANELLA, KAREN A

ART UNIT	PAPER NUMBER
1642	20

DATE MAILED: 06/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/328,296	Siegall et al
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is FINAL. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9, 21-25, 34-36, 38, 39, 42-44, and 47-91* is/are pending in the application.

4a) Of the above, claim(s) *35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9, 21-25, 34, 36, 38, 39, 42-44, and 47-91* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *Feb 28, 2002* is/are a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some* c)☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *19*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Response to Amendment

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

2. Claims 40, 41, 45 and 46 have been canceled. Claims 1, 4, 6, 8, 9, 21-24, 36, 44, 47-54 have been amended. Claims 1-9, 21-25, 34-36, 38, 39, 42-44 and 47-91 are pending. Claim 35, drawn to a non-elected invention, remains withdrawn from consideration. Claims 1-9, 21-25, 34, 36, 38, 39, 42-44 and 47-91 are under consideration.

3. The amendment filed February 28, 2002 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

Claims 21, 22, 23, 24, 47, 48, 51, 52 and 69 have been amended to read on increasing the binding of CD40 ligand to the cell surface CD40 on B cells by "at least 45%". However, the specification as originally filed recites (page 54, lines 15-18) that the increase in CD40 ligand binding afforded by the S2C6 antibody complexed to Ramos B cell surface CD40 was 51% to 68%". This is not sufficient support for the amendment of claims to read on an increase in the binding of CD40 ligand to the cell surface CD40 of B cells by at least 45%.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections Withdrawn

4. The rejection of claims 9, 21-25 and 36 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the monoclonal antibody S2C6 and fragments thereof, does not reasonably provide enablement for a protein comprising one or more

substitutions or insertions in the primary amino acid sequence relative to that of the monoclonal antibody S2C6, or a protein variant of S2C6, is withdrawn in light of applicants amendments..

5. The rejection of claims 1, 6, 8, 9, 21, 22, 23, 24, 44, and 45 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention due to lack of deposit information, is withdrawn in light of Exhibit C.

New Grounds of Rejection

6. Claims 36, and 61 in part rejected under 35 U.S.C. 103(a) as being unpatentable over Hirano et al (Blood, May 1999, Vol. 93, pp. 2999-300, cited in a previous Office action) in view of Pound et al (International Immunology, January, 1999, Vol. 11, pp. 11-20, reference BP of the IDS filed February 28, 2002). The instant claims are drawn to a pharmaceutical composition comprising a molecule that binds CD40, which molecule increases the binding of CD40 ligand to CD40 receptor on B-cells, CD40 ligand and a pharmaceutically acceptable carrier.

Hirano et al teach he inhibition of human breast carcinoma cells by soluble CD40 ligand. Hirano et al further teach that preliminary data indicates that ovarian carcinomas and bladder carcinomas are also inhibited in vitro by the CD40 ligand , suggesting that CD40 stimulation may be beneficial in the treatment of these tumors in vivo (page 3006, first column, lines 13-22). Hirano et al teach that the antiproliferative effects of the CD40 ligand is due to the induction of apoptosis and necrosis in cancer cells (page 3004, first column , last sentence of the paragraph headed "srhCD40L induces apoptosis in human breast carcinoma cells"). Hirano et al teach the concept of Activation Induced Cell Death (AICD) wherein signals which cause activation in normal cells result in growth-inhibition of transformed cells (page 3004, first column , first two sentences of the paragraph headed "srhCD40L induces apoptosis in human breast carcinoma

cells"). Hirano et al suggest a composition comprising an anti-CD40 monoclonal antibody and CD40 ligand, wherein the anti-CD40 antibody is not an antagonist of the CD40 receptor in order to assess synergism between the CD40 ligand and the anti CD40 antibody (page 3006, first column, lines 6-12).

Pound et al teach the monoclonal antibody of 5C3 which increases the binding of the CD40 ligand to the CD40 receptor on T-cells (Table 1). It is reasonable to conclude that the epitope of the T-cell CD40 receptor responsible for the interaction with the 5C3 antibody is present as the same epitope at the same location on the B-cell CD40 receptor. It is also reasonable to conclude that the epitope of the T-cell CD40 receptor responsible for the interaction with the CD40 ligand is also present as the same epitope at the same location on the B-cell CD40 receptor. Therefore, it is reasonable to conclude that 5C3 antibody would increase the binding of the CD40 ligand to the CD40 B cell receptor as the CD40 receptor does not differ in structure when expressed on B cells versus T cells . Thus, Pound et al teach that 5C3 is an agonistic antibody with respect to the activation of the CD40 receptor by CD40 ligand as 5C3 antibody increases the binding of CD40 ligand to the CD40 receptor.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the 5C3 antibody with the CD40 ligand in a pharmaceutical composition for the treatment of breast, ovarian and bladder carcinomas. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Hirano suggesting the combination of CD40 ligand with an antibody which activates the CD40 receptor for the treatment of solid tumors such as breast, ovarian and bladder carcinomas, and the teachings of Pound et al on the 5C3 antibody which increases the binding of CD40 ligand to the CD40 receptor.

7. Claims 36, 61 and 69-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hirano et al and Pound et al as applied to claims 36 and 61 above, and further in view of deBoer (US 5,874,082, cited in a previous Office action).

The specific embodiments of claims 36 and 61 are set forth above. Claims 69-71 are drawn to an antibody that binds to CD40, increases the binding of CD40 to cell surface CD40 on B cells by at least 45% and comprises a human immunoglobulin constant domain.

Pound et al teach the antibody of 5C3 which increases the binding of CD40 ligand to the CD40 receptor on T or B cells for the reasons set forth in the above section. Hirano et al teach the motivation for administering said antibody to treat breast, ovarian and bladder carcinomas, for the reasons set forth in the above section. Neither Pound et al nor Hirano et al teach the humanization of the 5C3 antibody.

DeBoer et al teach the humanized monoclonal antibodies of 5D12, 3A8 and 3C6 which bind to CD40 receptor and the efficacy of administering humanized anti-CD40 monoclonal antibodies versus murine antibodies in the treatment of human diseases (column 4, lines 14-19).

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to humanize the 5C3 antibody for administration to humans. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of deBoer et al on the desirability of avoiding HAMA responses during therapy and the improvements associated with the administration of humanized antibodies versus murine antibodies in the treatment of human diseases.

8. Claims 4, 5, 38, 62, 80, 81, 83, 84, 85 and 89-91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Francisco et al (Journal of Biological Chemistry, 1997, vol. 272, pp. 24165-24169) in view of Paulie et al (Journal of Immunology, 1989, Vol. 142, pp. 590-595). Claim 4 is drawn to a molecule comprising SEQ ID NO:8, 9 and 10, wherein said molecule binds CD40 and is a fusion protein comprising a second molecule which is not an antibody. Claim 5

embodies the molecule comprising the amino acid sequence of byodin fused to SEQ ID NO:7 fused to SEQ ID NO:2. Claim 38 embodies a pharmaceutical composition of the molecules of claims 1, 2, 3, 4, 5 or 6. Claim 62 is drawn to the pharmaceutical composition of claim 38, wherein the molecule is purified. Claim 80 is drawn to a molecule which comprises SEQ ID NO:7 and a single chain Fv. Claim 81 embodies the molecule of claim 80 conjugated to a chemotherapeutic agent. Claim 83 is drawn to a protein comprising an amino acid sequence having at least 80% identity to regions of a molecule comprising SEQ ID NO:8, 9 and 10, wherein said molecule binds CD40 and is a single chain Fv. Claim 84 specifies that the molecule of claim 83 comprises SEQ ID NO:8, 9 or 10. Claim 85 specifies the molecule of claim 83 wherein said molecule comprises at least 2 CDR sequences selected from the group consisting of SEQ ID NO: 8, 9 and 10 and comprising a human immunoglobulin constant domain. Claims 89-91 embody the molecules of claims 4, 83 and 87, wherein the molecules are fused to bryodin.

The specification teaches that SEQ ID NO:8, 9 and 10 are the amino acid sequences of the CDRs of the S2C6 antibody, and that SEQ ID NO:2 and 7 are the variable regions of the S2C6 antibody. Thus the invention of claims 4, 5, 38, 62, 80, 81, 83, 84, 85 and 89-91 is a protein comprising the variable regions or the CDR regions of the S2C6 antibody fused to non-antibody sequences, specifically bryodin or chemotherapeutic agents, and pharmaceutical compositions comprising the bryodin fusion proteins.

Francisco et al teach immunotoxins comprising the variable light chain region of the G28-5 antibody fused to the variable heavy chain region of the G28-5 antibody, wherein said single chain Fv was fused either to bryodin at the N-terminus (BD1-G28-5 sFv) or fused to the pseudomonas exotoxin at the carboxyl terminus (G28-5sFv-PE40). Francisco et al teach that these single chain immunotoxins were derived from the G28-5 antibody which binds the CD40 receptor. Francisco et al teach that lung, breast, colon and ovarian carcinomas were sensitive to G28-5sFv-PE40 (table 1), whereas B-lineage malignancies were sensitive to both G28-5sFv-PE40 and BD1-G28-5

sFv. (Page 24168, first column, second paragraph and figure 5). Francisco et al do not teach fusion proteins comprising the CDRs or variable regions of the S2C6 antibody.

Paulie et al teach the S2C6 antibody binds the CD40 receptor at a proximal epitope to that bound by the G28-5 antibody (abstract). Paulie et al further teach that the S2C6 and the G28-5 antibodies showed very similar binding with respect to some 24 cell lines tested (page 592, second column last line to page 593, first column, line 4). Francisco et al teach that the G28-5 antibody binds to CD40 receptor on B-lineage malignancies. Thus it is reasonable to assume that the S2C6 antibody will bind to the CD40 receptor on B-lineage malignancies.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the variable heavy and light chains of the S2C6 antibody for the variable heavy and light chains of the G28-5 antibody in both the G28-5sFv-PE40 and BD1-G28-5 sFv constructs taught by Francisco et al. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Paulie et al on the binding of the S2C6 and G28-5 antibodies to proximal epitopes on the CD 40 receptor, and the teachings of Francisco et al on the binding of the G28-5 antibody to the CD40 receptor on B-lineage malignancies.

9. Claims 1-9, 21-25, 34, 38, 39, 42-44 and 47-91 rejected under 35 U.S.C. 103(a) as being unpatentable over Francisco et al and Paulie et al as applied to claims 4, 5, 38, 62, 80, 81, 83, 84, 85 and 89-91 above, and further in view of Hirano et al (Blood, May 1999, Vol. 93, pp. 2999-300) and deBoer (US 5,874,082, cited in a previous Office action) and Riechmann et al (Nature, 1988, Vol. 332, pp. 323-327) and Greenwood et al (Effector function of matched sets of recombinant human IgG subclass antibodies. Pages 85-100, in: Protein Engineering of Antibody Molecules for Prophylactic and Therapeutic Applications in Man, Mike Clark, Ed., 1993). The instant claims are drawn to a protein comprising the variable region of the S2C6 antibody in addition to a human immunoglobulin constant domain. Additional embodiments include the

competition for binding to CD40 with the monoclonal antibody of S2C6, the increase in binding of CD40 ligand to CD 40 receptor by at least 45%, pharmaceutical compositions comprising said antibody and further comprising the CD40 ligand. Claim 34 specifies an antibody which is not isotype IgG1. For the reasons stated above, Paulie et al and Francisco et al render obvious a fusion protein comprising the variable chains of the S2C6 antibody for the treatment of B-cell malignancies. Neither Paulie et al not Francisco et al teach a protein comprising the variable chains of the S2C6 antibody and further comprising a human immunoglobulin constant domain, a pharmaceutical composition comprising said protein and the CD40 ligand , or the antibody which is not isotype IgG1.

Hirano et al teach that while contacting breast carcinoma cells in vitro with anti-CD40 antibodies did not result in the inhibition of growth of said cells, administering anti-CD40 antibodies to SCID mice bearing transplanted breast carcinoma cells resulted in significant anti-tumor effects attributed to the induction of antibody-dependent cell-mediated cytotoxicity in vivo (page 3005, first column, line 5 to page 3006, first column, line 2). The antibody administered to the SCID mice was murine in origin, having a murine constant region. Hirano et al suggest a composition comprising an anti-CD40 monoclonal antibody and CD40 ligand, wherein the anti-CD40 antibody is not an antagonist of the CD40 receptor in order to assess synergism between the CD40 ligand and the anti CD40 antibody (page 3006, first column, lines 6-12).

Riechmann et al teach that human immunoglobulin constant domains were more effective than murine immunoglobulin constant domains in antibody-dependent cell-mediated cytotoxicity effected by human cells. Greenwood et al teach the human isotypes of IgG1, IgG2, IgG3 and IgA are able to effect ADCC.

DeBoer et al teach the humanized monoclonal antibodies of 5D12, 3A8 and 3C6 which bind to CD40 receptor , the method for humanizing said antibodies and the efficacy of administering humanized anti-CD40 monoclonal antibodies versus murine antibodies in the treatment of human diseases (column 4, lines 14-19).

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to make a protein comprising the light and heavy variable chains of the S2C6 antibody fused to a human immunoglobulin constant domain which was not IgG1, and to use said protein in a composition with the CD40 ligand. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Francisco et al and Paulie et al which render obvious a fusion protein comprising the light and heavy variable chains of the S2C6 antibody, for the reasons set forth in the section above, and the teachings of Hirano et al on the anti-tumor effects of murine anti-CD40 antibodies against breast carcinoma cells transplanted in SCID mice, said anti-tumor affects attributed to ADCC; the suggestion of Hirano et al for a composition comprising an anti-CD40 monoclonal antibody and CD40 ligand, and the teachings of DeBoer et al, Greenwood et al and Riechmann et al on humanized CD40 antibodies, Greenwood et al on the ability of immunoglobulin isotypes other than IgG to mediate ADCC and Riechmann et al on the function of human constant domain in ADCC.

10. The instant references do not teach SEQ ID NO: 2, 7, 8, 9 or 10, or , with the exception of Pound et al as applied to the 5C3 antibody, the increase in binding of CD40 ligand to the CD40 receptor by at least 45%, by the claimed protein comprising the variable regions of the S2C6 antibody. The examiner maintains these specific embodiments are inherent in the antibody comprising the variable regions of the single chain S2C6 antibody fused to a human immunoglobulin constant domain or fused to bryodin or a chemotherapeutic agent. Applicants argue that inherent attributes of the claimed proteins cannot be properly used in a rejection under 35 U.S.C. 103(a). This has been carefully considered but not found persuasive.

"In determining whether the invention as a whole would have been obvious under 35 U.S.C. 103, we must first delineate the invention as a whole. In delineating the invention as a whole, we look not only to the subject matter which is literally recited in the claim in

question... but also to those properties of the subject matter which are inherent in the subject matter and are disclosed in the specification. . . Just as we look to a chemical and its properties when we examine the obviousness of a composition of matter claim, it is this invention as a whole, and not some part of it, which must be obvious under 35 U.S.C. 103." In re Antonie, 559 F.2d 618, 620, 195 USPQ 6,8 (CCPA 1977). The instant invention, as a whole, is a protein comprising the variable regions of the S2C6 antibody fused to either a human immunoglobulin constant region or a toxic or chemotherapeutic agent. Inherent in the properties of the claimed protein is the ability of said protein to increase the binding of CD40 ligand to the B-cell CD40 receptor by 51-68% (page 54, lines 15-18). As recited in the rejections above, there is sufficient motivation to combine the prior art references to anticipate the claimed invention, without knowledge of the requirement of "increasing the binding of the CD40 ligand to the CD40 receptor" or knowledge of the recited sequence identifiers. The court determined in In re Rijckaert, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993) that obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. However, the motivation to combine the prior art references is not predicated on increasing the binding of CD40 ligand to the CD40 receptor by at least 45%, or the recited sequence identifiers. Consequently, the prior art rejections are proper.

11. All other rejections and objections as recited in Paper No. 15 are withdrawn.

Conclusion

12. Applicant's amendment and submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on February 28, 2002 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a) and MPEP § 609(B)(2)(i).. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

ANTHONY C. CAPUTA
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Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
May 20, 2002